# PATENT COOPERATION TREATY 09/622101

From the:
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:
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19. Jan. 2000
Frist bearb.: 17.4. 17.7.00

# PCT

## WRITTEN OPINION

(PCT Rule 66)

| | |
|---|---|
| Date of mailing *(day/month/year)* | 17.01.2000 |
| Applicant's or agent's file reference: B 3270 PCT | **REPLY DUE** **within 3 month(s)** from the above date of mailing |

| International application No. | International filing date *(day/month/year)* | Priority date *(day/month/year)* |
|---|---|---|
| PCT/EP99/00945 | 12/02/1999 | 13/02/1998 |

International Patent Classification (IPC) or both national classification and IPC
C12P21/00

Applicant
MAX-PLANCK-GESELLSCHAFT ZUR FÖRDERUNG DER WISSENSC

1. This written opinion is the **first** drawn up by this International Preliminary Examining Authority.

2. This opinion contains indications relating to the following items:

| | | |
|---|---|---|
| I | ☒ | Basis of the opinion |
| II | ☐ | Priority |
| III | ☐ | Non-establishment of opinion with regard to novelty, inventive step and industrial applicability |
| IV | ☐ | Lack of unity of invention |
| V | ☒ | Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement |
| VI | ☐ | Certain document cited |
| VII | ☐ | Certain defects in the international application |
| VIII | ☐ | Certain observations on the international application |

3. The applicant is hereby **invited to reply** to this opinion.

**When?** See the time limit indicated above. The applicant may, before the expiration of that time limit, request this Authority to grant an extension, see Rule 66.2(d).

**How?** By submitting a written reply, accompanied, where appropriate, by amendments, according to Rule 66.3. For the form and the language of the amendments, see Rules 66.8 and 66.9.

**Also:** For an additional opportunity to submit amendments, see Rule 66.4.
For the examiner's obligation to consider amendments and/or arguments, see Rule 66.4 bis.
For an informal communication with the examiner, see Rule 66.6.

**If no reply is filed**, the international preliminary examination report will be established on the basis of this opinion.

4. The final date by which the international preliminary examination report must be established according to Rule 69.2 is: 13/06/2000.

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## I. Basis of the opinion

1. This opinion has been drawn on the basis of (*substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this opinion as "originally filed".*):

**Description, pages:**

1-64 as originally filed

**Claims, No.:**

1-38 as originally filed

**Drawings, sheets:**

1/7-7/7 as originally filed

2. The amendments have resulted in the cancellation of:

☐ the description, pages:
☐ the claims, Nos.:
☐ the drawings, sheets:

3. This opinion has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

4. Additional observations, if necessary:

## V. Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

| | | |
|---|---|---|
| Novelty (N) | Claims | 1-38 (Yes) |
| Inventive step (IS) | Claims | 1-38 (No) |
| Industrial applicability (IA) | Claims | 1-38 (Yes) |

2. Citations and explanations

**se s parate sheet**

1. The problem underlying the present application, the so-called "bottle-neck" of AZT activation, has already been described in the following publications:
   **PNAS, 1998, 95, 14045-14050 (D1),**
   **Biochemistry, 1998, 37, 3677-3686 (D2),**
   **Nature Structural Biology, 1997, 4/8, 601-604 (D3)** and
   **Nature Medicine, 3/8, 1997, 836-837 (D4).**

   **D1-D4** also describe the structural modifications occurring in the thymidylate kinase during the phosphorylation of AZT and they elucidate the function and the importance of the LID region , the P-loop or the amino acid in position 105 (see for instance, **D1**, page 14046, right column, 10 lines from the bottom) by comparison between the yeast or human and E. coli enzyme.
   Furthermore, **D3** suggests on page 603 (middle column) the modification of the thymidylate kinase, so that it phosphorylates AZTMP more effectively.

2. Therefore, not only the problem was described in the prior art, as demonstrated by **D1-D4**, but also the solution was suggested and even more the molecular basis for said suggestion was explained.
   As a consequence, the subject-matter of the present application cannot be considered as being based on an inventive concept and, hence, cannot give rise to claims allowable under Article 33.3 PCT.

3. The methods of claims 29 and 30 cannot be considered as inventive (Article 33.3 PCT), since they are only based on the well-known action of thymidylate kinases and are not depending on the modified kinases of the present application (Article 33.3 PCT).

4. Inhibitors, which are **obtainable** by the method of claims 31 or 32, but which have been obtained by other means, are already known. They could be for instance, a substrate analog, such as $TP_5A$. Therefore, claim 35 does not seem to be inventive (Article 33.3 PCT).

5. Rejection of the present application for lack of inventive step (Article 33.3 PCT) has to be expected.

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## Correspondence with the EPO on PCT Chapter II demands

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One of these labels should be affixed to a prominent place in the upper part of the letter or form etc. which you are filing.

**PCT** WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 :
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Published
*With international search report.*

(88) Date of publication of the international search report:
28 October 1999 (28.10. 99)

(54) Title: NOVEL MEANS AND METHODS FOR THE PREPARATION AND ACTIVATION OF NUCLEOSIDE AND NUCLEOTIDE BASED DRUGS

(57) Abstract

Described are novel means and methods for the preparation and activation of nucleoside and nucleotide based drugs. In particular, a method for the production of a polypeptide having or having enhanced kinase activity for a nucleoside or nucleotide analog is provided and polypeptides obtainable by said method. Described are also polynucleotides and vectors encoding said polypeptide obtainable by the method of the invention as well as to host cells transformed therewith. Furthermore, antibodies against said polypeptide are provided and pharmaceutical and diagnostic compositions as well as kits comprising proteins having kinase activity for a nucleoside or nucleotide analog or their encoding polynucleotides or vectors. Furthermore, the use of the before described proteins, polypeptides, polynucleotides, vectors and antibodies is provided for the preparation of pharmaceutical compositions for treating, preventing and/or delaying a disease related to viral infection or cancer. In addition, a method for identifying inhibitors of nucleoside or nucleotide kinases is described and methods for identifying nucleoside or nucleotide based prodrugs employing the above mentioned polypeptides, polynucleotides, vectors and host cells. Also provided are compounds identifiable by said methods as well as pharmaceutical and diagnostic compositions comprising said inhibitors. Moreover, the use of proteins and polypeptides having nucleoside or nucleotide kinase activity or their encoding polynucleotides or vectors is described for the preparation of nucleoside or nucleotide phosphates or analogs and derivatives thereof.